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Treatment of hypertension after renal transplantation: Long-term efficacy of verapamil, enalapril, and doxazosin

Alberto Martínez-Castelao, Miquel Hueso, Verónica Sanz, Javier Rejas, Jeroni Alsina, and Josep M. Grinyó

Nephrology Department, Hospital de Bellvitge Principes de España, CSUB, Hospitalet Llobregat, and Department of Medicine, University of Barcelona, Barcelona, Spain

Treatment of hypertension after renal transplantation: Long-term efficacy of verapamil, enalapril, and doxazosin. Normal blood pressure is a good marker of graft survival after renal transplantation, and effective antihypertensive treatment reduces the progression of graft damage. We conducted a long-term follow-up study of 88 hypertensive renal transplant recipients, all of whom were taking sustained cyclosporine A (CsA) immunosuppression. The patients were treated for at least three years, and initially received 240 mg/day of verapamil ($N = 24$, group I), 5 mg/day of enalapril ($N = 24$, group II) or 1 mg/day of doxazosin ($N = 40$, group III). Baseline creatinine did not differ in the three groups, but proteinuria was higher in the enalapril group (7 patients had proteinuria >1.5 g/day). Treatment was withdrawn in 5 patients in the verapamil group, 5 in the enalapril group and 2 in the doxazosin group due to drug-related side effects. Blood pressure (BP) control at three years was equivalent in the three groups (systolic BP, group I 157 ± 12; group II 149 ± 19; group III 154 ± 21; diastolic BP, group I 90 ± 8.7, group II 84 ± 9.8, group III 90.5 ± 16; mean BP, group I 113 ± 7, group II 106 ± 10, group III 106 ± 29). Two patients in group I, 3 in group II and 15 in group III required additional antihypertensive drugs. CsA levels increased in the verapamil-treated patients, allowing for an early decrease in CsA doses (1 year doses, 3.3 ± 1 mg/kg body wt/day in group I, 4.3 ± 1.6 in group II, 3.7 ± 1.6 in group III). Six cardiovascular events occurred, 3 in group I, 1 in group II, and 2 in group III patients. One patient died in the enalapril group and another in the doxazosin group. Eight verapamil-treated patients, 8 enalapril-treated patients and 4 doxazosin-treated patients lost their grafts due to biopsy-proven chronic transplant nephropathy. In conclusion, the three antihypertensive agents are effective in reducing blood pressure, with no clear advantage of one above any other. Verapamil allows the CsA dose to be reduced, thus decreasing the cost of immunosupression. Enalapril can be a more effective antiproteinuric agent, but hyperkalemia or impaired allograft function may occur in patients with non-optimal allograft function. Doxazosin offers an excellent safety and efficacy profile, and when not efficient by itself in controlling blood pressure, is an ideal concomitant agent in hypertensive renal transplant patients.

Key words: post-transplant hypertension, cyclosporine, calcium channel blockers, ACE inhibitors, alpha blockers, blood pressure, graft survival.

Hypertension after renal transplantation is an important factor in cardiovascular mortality in children and adults alike [1, 2], as well as a risk factor for graft loss [3]. It has not been established whether this is due to the deleterious effect of hypertension on the graft or if hypertension is a marker of an underlying disease [3].

The incidence of hypertension in the pre-cyclosporine era is estimated to be 40 to 50% of the renal transplant recipients [4, 5]. Introduction of cyclosporine has increased the prevalence of hypertension in the recipients of a solid organ transplant, which ranges from 60% to 80% of renal transplant patients, and up to 90% of non-renal transplant patients [6, 7]. Comparing the incidence of hypertension in patients treated with cyclosporine and azathioprine, Jarowenko et al found that the prevalence of hypertension was 63% in patients treated with cyclosporine versus 42% in the azathioprine group [6]. In the Cambridge University study [7], the incidence of hypertension was 67% in cyclosporine-treated patients versus 46% in azathioprine-treated patients. After switching from cyclosporine to azathioprine, the incidence of hypertension decreased significantly.

Post-transplant hypertension has multiple causes and mechanisms [8]. Usually, patients have more than one of the identified causes of hypertension, and some patients have all of the known causes [9]. In the early post-transplant period, a positive imbalance of sodium and water, acute tubular necrosis, acute ureteral obstruction, acute rejection episodes, high steroid doses, renal artery stenosis or hypercalcemia are factors that have been implicated in the early production of hypertension [10].

Hypertension after the three first months of transplantation may have other different causes. Steroids [11], cyclosporine nephrotoxicity [12] and tacrolimus [13] have been implicated as significant hypertensive factors. Steroid reduction to less than 10 mg/day, alternate day dosing or total steroid withdrawal [11] have decreased the incidence of hypertension.

After the introduction of cyclosporine, chronic rejection has persisted as an important factor for graft losses. The

transplanted renal mass or minor differences between the donor and recipient's body surface area have been reported as predictive factors for the development of chronic transplant nephropathy and post-transplant hypertension [14].

Renal artery stenosis [8, 9], renin-dependent hypertension [15] and *de novo* or recurrent nephropathies are responsible for some cases of post-transplant hypertension. A kidney transplanted from a cadaveric donor with familial essential hypertension can induce post-transplant hypertension [16]. More rare causes of post-transplant hypertension are the coexistence of a primary aldosteronism, a pheocromocytoma, or hypercalcemia due to a persistent hyperparathyroidism [9].

Whatever the cause of post-transplant hypertension might be, it seems clear that normal blood pressure is a good marker of graft survival, and that an effective antihypertensive treatment reduces the progression of graft damage [9]. Even if hypertension was only a consequence and not the cause of allograft dysfunction, it would still require therapy because of its known benefit on the cardiac and cerebral vascular systems [10]. Hypertension is a well-recognized risk factor for atherosclerotic vascular disease, which is the leading cause of long-term mortality in renal transplant patients.

Calcium channel blockers are good antihypertensive agents, decreasing preglomerular vasoconstriction. In addition, verapamil can improve cyclosporine nephrotoxicity. Angiotensin-converting enzyme (ACE) inhibitors have renoprotective effects, decreasing glomerular overload and proteinuria. Alpha blockers are effective in controlling high blood pressure with no metabolic interactions. Based on the known beneficial effects of these agents in the general population, the aim of our study was to compare the long-term efficacy of three different antihypertensive therapies on the outcome of grafts and patients in our kidney transplant patients, examining the metabolic and general tolerance of these regimes.

METHODS

Patients

We studied the long-term evolution of 88 renal transplant patients, divided into three groups, all of whom were under sustained CsA-based immunosuppression. All patients were hypertensive, as defined by WHO criteria for patients with some associated risk factors: systolic blood pressure (SBP) greater than 140 mm Hg or diastolic blood pressure (DBP) greater than 90 mm Hg.

Table 1 shows the patients' characteristics. The cause of end-stage renal failure did not differ in the three groups. Renal artery stenosis was ruled out based on a Doppler ultrasonography or a digital subtraction angiography. Patients in groups I and II were randomized to verapamil or enalapril, but patients with proteinuria over 1.5 g/day were included in the enalapril group. At baseline and every three months thereafter we measured plasma creatinine, total cholesterol, glycemia, uricemia, hematocrit, CsA levels, (specific monoclonal RIA), and prednisone doses, as well as the doses of the different antihypertensive treatments. The average values of three SBP and DBP measurements were recorded, and the mean blood pressure was calculated. Results are expressed at one, two and three years after treatment.

Table 1. Patient characteristics

	Group I ($N = 24$)	Group II ($N = 24$)	Group III ($N = 40$)
Age	43 ± 8.6	41 ± 9.7	44.5 ± 11
Sex males	14/10	16/8	24/16
Weight *kg body wt*	62.4 + 9	68.4 ± 14	68 ± 11
Height *cm*	163 ± 9	164 ± 7	163 ± 8
BMI *kg body wt/cm²*	23.7 ± 3	25.3 ± 4	25.4 ± 4
ESRD cause:			
Chronic GN	12	8	16
Polycystic RD	2	5	8
Chronic interstitial nephritis	3	4	6
N. angiosclerosis	3	3	5
Others	4	4	5
Time after transplantation	24 ± 12	25 ± 13	20 ± 12
Acute rejection episodes	3 (16%)	3 (16%)	6 (15%)

The patients were initially treated with slow release verapamil 240 mg/day (group I, $N = 24$), enalapril 5 mg/day (group II, $N = 24$), or doxazosin 1 mg/day (group III, $N = 40$). The initial doses were increased, and a second or a third antihypertensive drug was added, depending on blood pressure control.

Statistics

Statistical analysis was made by applying the Student's *t*-test to within-group measurements and the ANOVA (analysis of variance) to between-group comparisons.

RESULTS

The three groups of patients had similar baseline characteristics, except that proteinuria was higher in the enalapril group (Table 2). Body weight and body mass index changes were similar in the three groups. Systolic, diastolic and mean arterial blood pressure decreases were similar in the three groups over the years (Table 3). Plasma creatinine levels at one, two and three years were better in the doxazosin group, parallel to the lower level of proteinuria, than in the other two groups (Table 2). CsA levels increased after the introduction of verapamil in this group of patients, so that CsA doses could be decreased more rapidly in these patients than in the other two groups.

Hypercholesterolemia was higher at baseline in the verapamil and the enalapril groups (6.5 ± 1.2 in group I, and 6.56 ± 1.2 mmol/liter in group II) than in the doxazosin-treated patients (5.5 ± 1.2 mmol/liter). During the course of the follow-up, 5 patients in the verapamil group, 12 patients in the enalapril group and 13 patients in the

Table 2. Plasma creatinine, proteinuria, and cyclosporine levels and doses

	Group I	Group II	Group III
Creatinine *μmol/liter*			
Baseline	196 ± 86	178 ± 59	183 ± 101
1 year	180 ± 95	194 ± 69	164 ± 59
2 years	210 ± 142	215 ± 117	176 ± 69
3 years	265 ± 221	193 ± 108	194 ± 74
Proteinuria *g/day*			
Baseline	0.86 ± 0.85	1.73 ± 2.2[a]	0.44 ± 0.45
1 year	1.38 ± 1.56	1.27 ± 1.6	0.4 ± 0.5
2 years	1.24 ± 1.09	1.57 + 2.03	0.38 ± 0.53
3 years	0.98 ± 1.4	1.27 ± 2.5	1.04 ± 2.79
CsA levels *g/day*			
Baseline	181 ± 81	156 ± 42	181 ± 86
1 year	151 ± 59	136 ± 53	163 ± 72
2 years	158 ± 39	172 ± 101	153 ± 60
3 years	141 ± 62	144 ± 9	123 ± 44
CsA doses *mg/kg body wt/day*			
Baseline	4.5 ± 2	4.3 ± 1.5	4.9 ± 2.7
1 year	3.3 ± 1[a]	4.3 ± 1.6	3.7 ± 1.6
2 years	3 ± 0.6	4.05 ± 1.2	3.5 ± 1.4
3 years	2.8 ± 0.5	4.09 ± 1.2	2.6 ± 1.3

Specific monoclonal RIA, $N = 100–250$ ng/ml.
[a] $P < 0.05$.

Table 3. Systolic, diastolic and mean blood pressure results

	Group I	Group II	Group III
Systolic blood pressure			
Baseline	171 ± 19	166 ± 18	168 ± 20
1 year	155 ± 19[a]	159 ± 18	154 ± 19[a]
2 years	154 ± 24[a]	149 ± 19[a]	145 ± 20[a]
3 years	157 ± 12[a]	149 ± 19[a]	154 ± 21[a]
Diastolic blood pressure			
Baseline	106 ± 6	100 ± 9	97 ± 14
1 year	92 ± 8[a]	94 ± 13[a]	88 ± 12[a]
2 years	90 ± 13[a]	88 ± 8[a]	83 ± 12[a]
3 years	92 + 8.7[a]	84 ± 9.8[a]	90.5 ± 16[a]
Mean blood pressure			
Baseline	127 + 7.7	122 ± 9.6	121 ± 13
1 year	113 ± 11[a]	116 ± 14[a]	110 ± 12[a]
2 years	112 ± 15[a]	108 ± 10[a]	104 ± 12[a]
3 years	113 ± 7[a]	106 ± 10[a]	106 ± 29[a]

[a] $P < 0.05$ within-group
P values are not significant between groups.

doxazosin group required statins due to persistent hypercholesterolemia above 6.5 mmol/liter. No differences were seen with regards to uric acid, glucose, hematocrit or potassium levels. Nevertheless, two enalapril-treated patients presented with hyperkalemia.

During the course of the follow-up, 7 patients in the verapamil group, 10 patients in the enalapril group and 15 patients in the doxazosin group required other antihypertensive drugs to control their blood pressure levels. The higher doses of initial antihipertensive drugs were 480 mg/day of verapamil, 40 mg/day of enalapril and 16 mg/day of doxazosin (Table 4).

With regards to the side effects of the different medications, verapamil was well tolerated, but 5 patients (20.8%) showed side effects (tachycardia, heart failure, relative hypotension) that forced us to stop the treatment. Enalapril induced side effects (cough, hyperkalemia, creatinine increase) in five patients (21%). Doxazosin was very well tolerated with only two patients (5%) requiring treatment discontinuation due to orthostatic hypotension.

Table 4. Complications and follow-up

	Group I	Group II	Group III
Treatment discontinued due to side effects	5 (21%)	5 (21%)	2 (5%)[a]
Addition of other antihypertensives	7	10	15
Statin treatment	5	12	13
Cardiovascular events	3	1	2
Treatment follow-up *months*	33 ± 31	35 ± 8	36 ± 13
Transplant follow-up *months*	85 ± 20	91 ± 22	59 ± 21
Graft loss	8 (33%)	8 (33%)	4 (10%)[a]

[a] $P < 0.05$ Group I and Group II vs. Group III

Six patients suffered cardiovascular events during the follow-up period. Graft survival was higher in doxazosin-treated patients; only 4 patients (10%) lost the graft, while 5 patients (21%) lost the graft in the verapamil group and 8 patients (33%) lost the graft in the enalapril group. One patient in the doxazosin group died suddenly (myocardial infartion?), and one in the enalapril group died from a hepatobiliary neoplasm.

DISCUSSION

It is likely that evidence of renal protective effects of specific antihypertensive agents in hypertension in the general population will apply to transplant patients despite the differences in the cause of hypertension [10].

In considering the renal effects of antihypertensive treatment, Mountokalakis stresses that several important questions arise [17]. Should the immediate or medium-term renal effects of antihypertensive treatment be distinguished from its long-term effects on renal prognosis? Is the potentially protective effect determined by changes in the systemic blood pressure? Can antihypertensive therapy delay the progression of an underlying renal disease? Does the ability of the antihypertensive therapy to protect the kidney depend on the particular antihypertensive agent used to lower blood pressure? What target blood pressure is required to preserve renal function?.

The need for a redefinition of a target blood pressure that would preserve renal function has been suggested by some authors. Recently, the Joint National Committee for the Detection, Evaluation and Treatment of High Blood Pressure recommended a target blood pressure of 135/85 mm Hg or less for patients with renal diseases [18].

Many studies have provided evidence that various antihypertensive agents exert disparate short-term or prolonged effects on renal hemodynamics [17]. ACE inhibitors

lower systemic blood pressure and glomerular capillary pressure, increasing renal blood flow by decreasing postglomerular arteriolar tone, that is, efferent vasodilation [19]. These agents might be more efffective than others in preventing the progression of renal damage, improved by additional pharmacological measures and by dietary sodium and protein restrictions, considering the risk factor profile [20].

Increased renal vascular resistance is a prominent feature of post-transplant hypertension [9, 10]. New agents that lower blood pressure and increase renal blood flow could be the ideal drugs to treat hypertension after renal transplantation. However, it is not clear whether preglomerular vessels are primarily affected, or if hypertension causes glomerular hypertension first and preglomerular hypertension serves as a secondary protective response [10]. Diuretics, beta blockers and alpha blockers have had a significant role in treating hypertension in kidney transplant patients. Often, nonspecific vasodilators and beta blockers decrease renal blood flow as a response to the reduction of systemic blood pressure, but it has not yet been shown whether long-term use of these agents will result in a poorer outcome than the use of the newer agents [21]. Since there is evidence that these new agents might slow the progression of chronic renal failure [22, 23], it is also possible that they may have a beneficial effect on chronic rejection.

Theoretically, calcium channel blockers might be a better choice than ACE inhibitors because they promote dilation in the afferent arteriole [3], which is the same location where cyclosporine induces vasoconstriction [24]. However, calcium channel blockers can frequently cause some undesirable side effects in transplanted patients, such as lower extremity edema, enhancement of cyclosporine hypertrichosis, and gingival hypertrophy.

Verapamil is a very well-known diphenyl-alkylamine derivative, effective in reducing blood pressure. When used by intravenous administration it can induce reflex tachycardia, increased cardiac output and peripheral vasoconstriction. It is recognized that verapamil can have a positive interaction with cyclosporine metabolism, that being the advantage of decreasing cyclosporine doses, as we have proven in our patients [25].

In our experience, verapamil was not tolerated in five patients in the early stage of the treatment. Long-term tolerance to verapamil has been good, but 8 patients (33%) in this group lost the graft, which was all due to chronic transplant nephropathy.

ACE inhibitors are also effective in controlling blood pressure in renal transplant recipients, and do not interact with cyclosporine blood levels. Its antiproteinuric effect is very useful in transplant recipients, so they can act as renal protective agents. On the negative side, they are associated with potassium retention. In our patients, ACE inhibitors caused long-term hyperkalemia and impaired graft function in 4 patients, and coughing in another. While they are very useful antihypertensive agents, careful monitoring of potassium levels and renal function is required, especially when used in patients with suboptimal graft function. Regarding the long-term results in our experience, 8 patients lost the graft in the enalapril-treated group due to chronic allograft nephropathy, which was the same percentage as in the verapamil group.

The blood pressure reduction with both types of agents, calcium channel blockers and angiotensin-converting enzyme inhibitors, is equivalent [26]. If indeed there are no clinical differences between these two groups of antihypertensive agents, this suggests that preglomerular vasoconstriction is an essential factor in such hypertension, rather than glomerular hypoperfusion [9].

These antihypertensive drugs can exert different actions on proteinuria. Recently, Gansevoort et al examined the results of 41 trials comparing the antiproteinuric effect of ACE inhibitors with that of other antihypertensive agents [27]. It seems that the most important antiproteinuric effect is conferred by ACE inhibitors, but there is some evidence that non-dihydropiridine calcium antagonists can decrease proteinuria regardless of blood pressure changes [28].

Alpha blockers such as doxazosin act by producing a peripheral vasodilating effect, reducing peripheral resistance and interfering with adrenergic vasoconstrictor mechanisms without interfering with regional flows, not decreasing cerebral, cardiac or renal plasma flow [29]. Doxazosin has not induced a deleterious effect on serum cholesterol and potassium or renal function. It is very well tolerated, and only orthostatic hypotension may be induced, especially with the first doses.

Patients treated with doxazosin have shown an excellent tolerance; only two patients were withdrawn from the study because of relative hypotension. The antihypertensive efficacy of doxazosin has been proven in our patients, but 15 patients in this group required a second antihypertensive agent. Regarding the long-term graft and patient survival in the doxazosin group, only 4 patients lost the graft and all of them were due to chronic transplant nephropathy.

A final comment about the impact of these antihypertensive regimes on the quality of life of hypertensive renal transplant patients must be added. When new drugs are compared, no clear advantage has been noted for any particular class of antihypertensive agent. It does not seem that calcium channel blockers, ACE inhibitors or alpha blockers would offer a different profile regarding quality of life of our hypertensive renal transplant patients.

In summary, the three groups of antihypertensive agents, ACE inhibitors, calcium channel blockers and alpha blockers, are effective in long-term reduction of blood pressure in renal transplant patients, with no clear advantages of any one over the others. The CsA-verapamil interaction may permit a reduction of cyclosporine doses and thus decrease

the cost of immunosuppression, but calcium channel blockers are associated with side effects in a low percentage of patients. ACE inhibitors offer the possibility to act as renal protectors, but cough, anemia, hyperkalemia or allograft function impairment are potential side effects requiring careful renal function monitoring, especially in cases of suboptimal renal function. Doxazosin offers an excellent tolerance profile, being a good alternative in monotherapy or in association with other antihypertensive drugs, owing to its safety and efficacy. It seems that doxazosin-treated patients have a similar long-term outcome as those patients who are treated with calcium channel blockers or ACE inhibitors.

Reprint requests to Alberto Martínez-Castelao, M.D., Nephrology Department, Hospital de Bellvitge Principes de España, CSUB, C/Feixa Llarga s/n, 08907 Hospitalet Llobregat, Department of Medicine, University of Barcelona, Barcelona, Spain.

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